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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,395	03/13/2007	John William Benbow	PC026073A	9039

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EXAMINER	
MURRAY, JEFFREY H	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
05/15/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/575,395	BENBOW, JOHN WILLIAM	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) *6-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

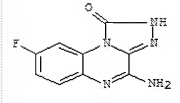
1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/28/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an election from a restriction requirement filed on March 25, 2009. There are twelve claims pending and five claims under consideration. Claims 6-12 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 25, 2009. This is the first action on the merits. The present invention relates to certain 2H-[1,2,4]triazolo[4,3-a]pyrazine-1-ones which are inhibitors of glycogen synthase kinase 3 (GSK-3) and, as such, are useful in the treatment of, *inter alia,* conditions, diseases, and symptoms such as diabetes, dementia, Alzheimer's Disease, bipolar disorder, stroke, schizophrenia, depression, hair loss, cancer, and the like.

2. Applicants have traversed and stated that the Mallet paper does not show any 8-amino-2H-[1,2,4]triazolo[4,3-a]pyrazine-3-ones. Examiner agrees with this statement concerning this particular paper. However, several other papers exist which do show this core structure in a compound, for example, Sarges, et. al., Journal of Medicinal Chemistry (1990), 33(8), 2240-54 which shows the following compound:

RN 127710-85-4 CAPLUS
CN [1,2,4]Triazolo[4,3-a]quinoxalin-1(2H)-one, 4-amino-8-fluoro- (CA INDEX NAME)



As stated in the original restriction requirement, the R^1, R^2, R^a and R^b variables can be a number of different groups, therefore they cannot be considered part of the "special technical feature" of the compound or composition. In this regard, these groups do not define a contribution over the prior art. This prior art shows a compound which has a fused phenyl ring as its R^1 and R^2 variables. Since the R^1 and R^2 variables have no special technical feature, this compound breaks the unity of invention. Therefore this restriction is considered proper and thus made **FINAL**.

Priority

3. Acknowledgment is made of applicant's claim to a national stage application. The current application, 10/575,395, filed on March 13, 2007, is a national stage application of PCT/IB03/03137, filed on September 27, 2004.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either an application data sheet or supplemental oath or declaration.

It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

Specification

5. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Objections

6. Claim 1 is objected to because of the following informalities:

Claim 1 is not in the singular, alternative format. It is suggested that applicant rewrite claim 1 to read, "...a prodrug thereof, or a pharmaceutically acceptable salt of the compound or prodrug, wherein...". No new matter permitted. Appropriate correction required.

Claim Rejections - 35 USC § 112, 1st paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a triazolopyrazine where R^1 and R^2 are hydrogen or alkyl, does not reasonably provide enablement for all of the other R groups listed nor

any prodrugs within the broad Claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See Ex parte Forman 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* The Applicant has demonstrated within the application how to make 8-amino-triazolopyrazines. However, there is no working example of any compounds with R groups other than previously mentioned nor has applicant demonstrated any prodrugs. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However...there is no evidence that such compounds exist...the examples of the '881 patent do not produce the postulated compounds...there is...no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that

prodrugs of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that prodrugs can be made, or limit the claims accordingly.

The quantity of experimentation needed to make or use the invention must be considered to determine if undue experimentation is present. With regard to quantity of experimentation needed, (note Wolff et. al., "Burger's Medicinal Chemistry and Drug Discovery," 5th Ed. Part 1, pp. 975-977 (1995) provided with this action), which emphasizes the many experimental factors for consideration for a successful prodrug as well as the difficulty in extrapolating data from one species to another. See p.975-7. "Extensive development must be undertaken to find the correct chemical modification for a specific drug. Additionally, once a prodrug is formed, it is a new drug entity and therefore requires extensive and costly studies to determine safety and efficacy." Banker, et. al., Modern Pharmaceuticals, p.596-7. In view of all these factors undue experimentation would be required to practice the invention.

2) *Unpredictability in the art.* It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out

> what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

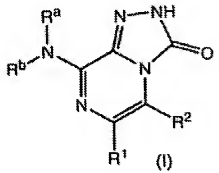
The scope of prodrugs is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. The choice of a prodrug will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which ester/amide will be suitable for the instant invention. The application does not provide any guidance for one skilled in the art on how the prodrug converted to active compounds, by what mechanisms and at what site the prodrug will be activated, what *in vivo* enzymes are likely involved in cleaving the protected group, etc.

Applicants provide no reasonable assurance that any and all known prodrugs will have the ability to regenerate in *vivo* to the instant compounds by one or more biological processes. It is not the norm that one can predict with any degree of accuracy a particular ester form of an active compound will be more soluble, more easily handled in formulations or more bioavailable without actual testing *in vivo*.

3) *Number of working examples.* The compound core depicted with specific substituents represents a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any compounds, compositions or pharmaceutically acceptable salts where the R variables were not those mentioned above in the present application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Scope of the claims.* The scope of the claims involves all of the tens of thousands of compounds of the following formula:



(I)

thus, the scope of claims is very broad.

5) *Nature of the invention.* The nature of this invention relates generally to certain 2H-[1,2,4]triazolo[4,3-a]pyrazine-1-ones which are inhibitors of glycogen synthase kinase 3 (GSK-3) and, as such, are useful in the treatment of, *inter alia,* conditions, diseases, and symptoms such as diabetes, dementia, Alzheimer's Disease, bipolar disorder, stroke, schizophrenia, depression, hair loss, cancer, and the like.

6) *Level of skill in the art.* The artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions or treating the diseases mentioned.

Claim Rejections - 35 USC § 112, 2nd paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 1 contains a discrepancy in its definition of R^1 and R^2. The substituents start with (ii) hydrogen, (iii) halogen, etc. and continue on. Examiner is unsure whether

the groups for R^1 and R^2 have been misnumbered, or if a substituent group which should properly be labeled (i) is missing. No new matter permitted. Appropriate correction is required.

12. The proper structure from the first structure name, 5-[2-(6-tert-butyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-8-ylamino)-nicotinic acid methyl ester; in Claim 4 cannot be ascertained due either a missing or extra bracket in the nomenclature. According to claim 1, R^2 cannot be a heteroaryl group, and this structure appears to have a nicotinic acid methyl ester as the R2 group. No new matter permitted. Appropriate correction is required.

Conclusion

13. Claims 1-5 are rejected.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on Mon.-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey H Murray/
Patent Examiner , Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624